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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,888	09/29/2003	Ellen W. Evans	oc01600	1648

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
ISSAC, ROY P	
ART UNIT	**PAPER NUMBER**
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/673,888	EVANS ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 6-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 6-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/17/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application claims priority under 35 U.S.C § 119(e) from the provisional application 60/414,948 filed on 9/30/2002.

This Office Action is in response to Applicant's response (remarks/Argument/ Amendment to the claims) filed 17 January 2007, wherein claims 2, 3, 6, 7, 9, 10, 12-15 and 17-18 were amended, claims 1, 4 and 5 were cancelled and new claims 19-29 were added.

Rejections Withdrawn

As indicated above, applicant's arguments/response filed 17 January 2007 cancelled claims 1, 4 and 5. All rejections made with respect to the cancelled claims, 1, 4 and 5, in the previous office action are withdrawn.

The objection under 37 CFR 1.75 with respect to claims 1 and 17 as substantial duplicates of each other is withdrawn, since claim 1 is cancelled.

The rejection under 35 USC 112 first paragraph, with respect to claims 1-18 in regards to scope of enablement for the prevention of hypercalcemia and for the treatment of any disorder associated with calcium homeostasis is withdrawn since the applicants have cancelled claim 1 and the amended claims do not recite prevention of hypercalcemia, and the claims as amended are directed to the treatment of specific disorders recited in claims 2 and 3.

The rejection under 35 USC 112 second paragraph, with respect to claims 1-18 is withdrawn since the phrase "disorder of calcium homeostasis" is deleted from claims 3, 17 and 18.

Claim Objections

Claims 10 and 23 are objected to because of the following informalities: Claims 10 and 23 appears to have trademarks/abbreviation (AMG 073, NPS 467 for example) in the claims. Applicant is advised that full chemical names should be used in claims. Under 35 U.S.C 112 it is improper to use an acronym without defining it first within claims. Where a trademark or trade name or abbreviation is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C 112, second paragraph. See *Ex parte Simpson,* 218 USPQ (Bd. App. 1982). Appropriate correction is required.

The following are new grounds for rejection necessitated by applicant's amendments:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 recites the limitation "wherein the level of Ca^{2+}" in lines 1-2, page 17. There is insufficient antecedent basis for this limitation in the claim.

The following are modified rejections necessitated by Applicant's amendment filed 1/17/2007, wherein the limitations in pending claims 2, 3, 6, 7, 9, 10, 12-15 and 17-18 have been changed, and new claims 19-29 have been added, and all claims depend from amended claims 2 and 3. The limitations in the amended claims have been changed and the breadth and scope of all claims have been changed. Therefore, rejections from the previous Office Action, filed 9/20/2006, have been modified and are listed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-16 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for one of the specific compounds listed in claim 2 and for the combination of said compounds with one of the compounds listed in claim 10, does not reasonably provide enablement for the use of a combination of a compound of formula I with **any** compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to the method for the treatment of disorders associated with calcium homeostasis. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The claimed invention is a therapeutic method for preventing or treating a disorder of calcium homeostasis.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The breadth of the claims:

The current claims are deemed very broad since they include the combination of any compound used for the treating one of the disorders listed in claim 9 with one of the compounds of formulas 1-81. The compound to be combined includes all known drugs used for the treatment of said diseases as well as the ones to be developed in the future.

The amount of direction or guidance presented and the presence or absence of working examples:

There are no methods or examples of using any compound other than the compound of Formula I is given. There are no examples or methods for the use of any compounds in combination with any compounds is given. The specification contains a general description of compounds to be used in combination therapy. (Specification, Page 22, lines 20-35). However, this description does not include any specific examples or any general guidelines as to how a combination is to be formulated to enable one of skill in the art to practice the invention without further experimentation.

The examples 1-2 relates to the study of toxicity of the compound of Formula I. Note that the compound of Formula I is a well-known pharmaceutical in clinical use. Example 2 involves the microscopic evaluation of rats that were given the compound of formula I, which shows that the parathyroid glands are affected by the administration of said compound. However, the examples do not

indicate that the rats were suffering from any particular disorders associated with calcium homeostasis.

There are no examples of the use of any other compound or any compound in combination with the compounds of Formula A for the treatment of any particular diseases associated with calcium homeostasis as claimed herein.

The predictability or lack thereof in the art and the quantity of experimentation necessary:

Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects, which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic

index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56. (PTO-892) Thus, the teachings of the book clearly support that the instant claimed invention, administering a combination of a compound of formulas 1-81 with any compound used for treating one of the disorders disclosed in claim 9 is highly unpredictable.

The usefulness of one compound to have an effect on the calcium homeostasis or for the treatment of one of diseases claimed herein, does not mean that compound and all similar compounds are useful for combination therapy with one of the known drugs used to treat such diseases.

In particular, one skilled in the art would need to know whether the regular administration of the combination in the claimed form over the long term would adversely affect the health of the subject.

In order to answer these questions, in the absence of any existing data, one skilled in the art, will have to undertake laboratory and clinical studies

involving different combinations of one of the compounds of formulas 1-81 and one of any of a large series of compounds used to treat one of the diseases listed in claim 9. Accomplishing such a task for the myriad of symptoms that can be considered associated with calcium homeostasis would require an undue amount of experimentation for the practice of full range of the claimed invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the combination therapy claimed herein absent undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-3, 6-8, and 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et. al. (Of Record) in view of Eskens et.al. (Of Record)

further in view of applicant's admission regarding the relation between farnesyl transferase inhibitors and disorders of calcium homeostasis. (Specification, Page 3, lines 8-15).

Doll et. al. discloses a series of compounds for the inhibition of Farnesyl transferase. (Page 1, lines 10-15, and Page 2 to 13). Tricyclic compounds of Formula A of the instant application are disclosed for their activity against farnesyl transferase. (Doll et. al, WO/97/23478; Page 15, lines 1-15 and; Page 2 line 10 to Page 13, line10). Doll et. al. further discloses the use of said compounds in patients and with pharmaceutically acceptable carriers. (Page 115, line 5 to Page 116 line 5). Doll et. al further discloses the use of compounds of Formula A for the treatment of a variety of cancers, including thyroid follicular cancer. (Page 116, lines 4-10). Doll et. al. further discloses tablet formation. (Page 88).

Doll et. al. does not explicitly disclose the use of compounds of Formula A for the treatment of familial benign hypocalciuric hypercalcemia, or neonatal severe primary hyperparathyroidism or renal secondary hyperparathyroidism or osteoporosis or malignancy associated hypercalcemia or humoral hypercalcemia of malignancy.

Eskens et. al. discloses that Ras oncogenes and Ras oncoproteins are found with high frequency in various human tumour types and that enzyme farnesyl transferase is involved in the activity of Ras. (Page 319, First Paragraph). One of the diseases associated with Ras tumours is malignancy associated hypercalcemia. (Eskens, Page 324, Column 1, Paragraph 4) B-

1086, a well known inhibitor or farnesyl transferase was found to induce a near normalization of malignancy associated hypercalcemia and elevated parathyroid related peptide levels in serum. (Eskens, Page 324, Column 1, Paragraph 4). Compound SCH 66336 is well known for its activity as an inhibitor of farnesyl transferase. (Eskens, Page 327, Figure 6 and Tables 1-2).

Applicant admits that 10-20% of cancer patients suffer from parathyroidism. (Specification, Background of the invention, Page 2, 17-25). Applicant further admits of the relation between Farnesyl protein and disorders associated with calcium homeostasis. (Specification, Page 3, lines 8-15). Farnesylation inhibitor B-1086 has been used to treat malignancy associated hypercalcemia. (Specification, Page 3, lines 8-15).

It would have been obvious to one of ordinary skill in the art to use compounds of Formula A and in particular the compound of Formula I for the treatment of disorders associated with calcium homeostasis. Furthermore, it would have been obvious to one of ordinary skill in the to use the specific compounds of Claim 18 because they are structurally similar to compounds of Formula A, well known for their activity against Farnesyl transferase.

One having ordinary skill in the art would have been motivated to do this because compounds of Formula A are well known for their inhibitory activity against Farnesyl transferase and Farnesyl transferase is well known for its involvement in disorders of calcium homeostasis. Furthermore, one of ordinary skill in the art would have been motivated the specific compounds of Claim 18

because they are structurally similar to compounds of Formula A, well known for their activity against Farnesyl transferase.

Claims 9-16 and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et. al. (Of Record) in view of Eskens et.al. (Of Record) further in view of applicant's admission regarding the relation between farnesyl transferase inhibitors and disorders of calcium homeostasis. (Specification, Page 3, lines 8-15), further in view of Nemeth et. al. (Of Record).

The disclosure of Doll et. al. is discussed above.

Doll et. al. does not explicitly disclose a combination of a compound Formula A with a second compound used for for the treatment of familial benign hypocalciuric hypercalcemia, or neonatal severe primary hyperparathyroidism or renal secondary hyperparathyroidism or osteoporosis or malignancy associated hypercalcemia or humoral hypercalcemia of malignancy.

Nemeth et. al. discloses the use of compounds NPS R-568, and NPS R-467 as useful for the treatment of calcium homeostasis related disorders. (Page 4040, Abstract). Nemath further discloses said compounds for the treatment of osteoporosis and hyperparathyroidism. (Page 4040, Column 2, Paragraph 3).

The disclosure of Eskens et. al. and the admissions in the specification are discussed above.

It would have been obvious to one of ordinary skill in the art to use compounds of Formula A and in particular the compound of Formula I in combination with another compound used for the treatment of disorders associated with calcium homeostasis including osteoporosis and

hyperparathyroidism, or to administer two drugs simultaneously or non-simultaneously. It is considered well within the capabilities basic skills of one of ordinary skill in the art to determine the time of administration of two drugs.

One having ordinary skill in the art would have been motivated to do this because compounds of Formula A are well known for their inhibitory activity against Farnesyl transferase and Farnesyl transferase is well known for its involvement in disorders of calcium homeostasis, and NPS R-568 and NPS R-467 are well known for the treatment of disorders associated with calcium homeostasis such as osteoporosis and hyperparathyroidism.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

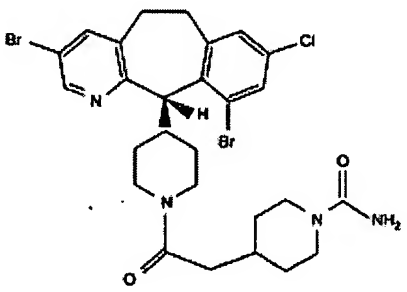
Thus, one of ordinary skill in the art would have reasonably expected that a composition comprising compounds of Formula A and NPS-R-568 and NPS-R-$67 would have had improved activity against disorders of calcium homeostasis. Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

No claim is allowed.

Response to Arguments

Applicant's arguments filed 1/17/2007, and the exhibits A-D, with respect to the above rejections under 35 U.S.C. 103(a), of record in the previous Office Action have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art as further discussed below.

Applicants argue that one of ordinary skill in the art would not have had a reasonable expectation of success in using any of the compounds 1-81 or the compounds set forth in claim 18 to treat familial benign hypocalciuric hypercalcemia, neonatal sever primary hyperparathyroidism, renal secondary hyperparathyroidism, osteoporosis, malignancy-associated hypercalcemia or humoral hypercalcemia of malignancy. However, Eskens et. al. discloses the use of farnesyl transferase inhibors (FTI) for the treatment of malignancy associated hypercalcemia. Eskens further discloses SCH 663336, one of the compounds listed in claim 2 herein as an FTI. The structure of SCH 66336 is shown below:



Since the examiner has not asserted that the compound B1086 is structurally similar to compounds of instant application, applicants arguments regarding a lack of structurally similarity between B1086 and compounds of

instant application is irrelevant. Based on Eskens disclosure of the relation between farnesyl transferase and malignancy –associated hypercalcemia, as well as the knowledge of one of ordinary skill in the art regarding the relationship between farnesyl transferase and malignancy associated hypercalcemia, one of ordinary skill in the art would have expected well known inhibitors of farnesyl transferase, including those of the instant application, would be effective against treating malignancy-associated hypercalcemia.

Applicants arguments regarding various anti-histamines is considered but found unpersuasive because both compounds with activity against histamine receptor are used against allergic reactions. Both Loratadine and diphenylhydramine act against allergic reactions by inhibiting histamine receptor. However, diphenylhydramine seems to be able to effect sedation as well, possibly through another receptor, not discussed in the arguments. Based on the ability of loratadine and diphenylhydramine to inhibit histamine receptor, one of ordinary skill in the art would have reasonably expected them to have anti-allergic properties. Similarly, once the relationship between farnesyl transferase and malignancy associated hypercalcemia is known, one of ordinary skill in the art would have reasonably expected that compounds that can inhibit farnseyl transferase will have activity against malignancy associated hypercalcemia. As such, the rejection under 35 U.S.C 103(a) is still deemed proper and is maintained.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4/6/07

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